Original Article

Effect of human acellular dermal matrix (Megaderm™) on infra-auricular depressed deformities, Frey's syndrome, and first bite syndrome following parotidectomy: a multi-center prospective study

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Background: Parotidectomy is the primary treatment for parotid gland tumors. However, complications may include a prominent facial scar or infra-auricular depressed deformity, Frey's syndrome, first bite syndrome, or other facial pain, numbness, and paralysis. Acellular dermal matrix (ADM) has been widely used to prevent these complications in parotid surgery, but there have been no prospective, multi-center trials documenting its efficacy. This study evaluates the effectiveness of ADM implantation in preventing infra-auricular depressed deformity, Frey's syndrome and first bite syndrome after parotidectomy.

Methods: We analyzed 51 cases of standard parotidectomy and 58 cases of parotidectomy with implantation of Megaderm™ ADM through prospective multicenter trial. Acute complications including infection, seroma, hematoma, skin necrosis, and acute parotid area pain were evaluated 1 week postoperatively. Clinician grading of Frey's syndrome and blinded clinician evaluation of infra-auricular depressed deformities were conducted at 3, 6, and 12 months. Patients evaluated subjective satisfaction with neck appearance, Frey's syndrome quality, and acute parotid area pain at 3, 6, and 12 months.

Results: There was a higher incidence of seroma in the Megaderm™ group than in the control group at week 1. The incidence and total clinician-evaluated Frey's syndrome scores were significantly lower in the Megaderm™ group than in the control group at 3, 6, and 12 months. Both the objective and subjective evaluations of the facial contour showed a better outcome in the Megaderm™ group compared to the control group at 3, 6, and 12 months. There were no significant differences between the groups in the patient-reported Frey's syndrome quality scores at 3, 6, and 12 months, but the Megaderm™ group reported significantly less acute pain than the control group.

Conclusions: ADM implantation can effectively reduce the occurrence of Frey's syndrome, infra-auricular depressed deformity, and first bite syndrome after parotidectomy. ADM may be especially advantageous in complex parotidectomy cases when significant complications are expected.

Keywords: Acellular dermal matrix (ADM); Frey's syndrome; first bite syndrome; parotidectomy

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Introduction

Parotidectomy is the primary treatment for parotid gland tumors. However, parotidectomy can cause considerable complications including a prominent facial scar or infra-auricular depressed deformity, gustatory sweating, facial pain, numbness and paralysis (1). Most parotidectomy patients, especially young women, are concerned about postoperative changes in facial appearance, which can have adverse effects on patients' mental status. Recently, the facial scar problem has been somewhat resolved with the modified facelift incision method (2). However, preventing an infra-auricular depressed deformity continues to be a challenge, particularly in total parotidectomy.

In addition, patients undergoing parotidectomy occasionally complain about flushing, sweating, or intense pain in the parotid region during food intake, which may be attributed to Frey's syndrome (3). It results from aberrant regeneration of parasympathetic nerve fibers within the parotid gland to the overlying sweat glands of the skin (4). Rarely, patients with parotidectomy suffer acute facial pain at the first bite of each meal, which is aptly termed "First bite syndrome" (5). All of these complications have negative effects on patients' quality of life.

Current surgical methods for preventing depressed deformities and Frey's syndrome include dermo-fat graft, temporalis myofascial flap, and sternocleidomastoid muscle flap (6-10). However, these autologous tissue transplantations have problems such as additional surgical donor site trauma, increased operating time, and a limited donor quantity (11). Since the early 1990s, acellular dermal matrix (ADM) has been developed and utilized for various head and neck reconstructions (12). ADM is obtained from human cadaver skin by solvent, detergent, and freeze-drying processes to eliminate cellular components (13). It consists of an extracellular matrix and basement membrane which is sterile and non-immunogenic.

In parotid surgery, ADM has proven useful for the space-occupying effect and prevention of Frey's syndrome (14,15). However, previous studies have shown insignificant results due to retrospective designs or small numbers of patients, and there have been no prospective and large-scale clinical trials for ADM use with parotid surgery. Therefore, we performed a multi-center prospective trial to evaluate the effectiveness of Megaderm™ ADM for the prevention of infra-auricular depressed deformities, Frey's syndrome, and first bite syndrome following parotid tumor surgery.

We present the following article in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/gs-20-703).

Methods

Study protocol

This multi-center prospective clinical trial was carried out at 6 tertiary head and neck centers (Ajou University Hospital, Cheonan Soonchunhyang University Hospital, Gangnam Severance Hospital, Inha University Hospital, International St. Mary's Hospital, and Severance Hospital).

The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards of Ajou University, Cheonan Soonchunhyang University, Gangnam Severance Hospital, Inha University, International St. Mary's Hospital, Severance Hospital and informed consent was taken from all individual participants.

Patients

Between November 2015 and March 2018, patients with benign parotid tumors who underwent superficial or total parotidectomy by experienced head and neck surgeons were considered eligible. The exclusion criteria ruled out patients who were younger than 18 or older than 70 years, had a malignant tumor at final histology, a history of keloid scarring, a current pregnancy, recurrent parotid tumors, previous parotid surgery, or an uncontrolled medical illness.

Surgical procedure

A modified facelift incision method was used through the skin, subcutaneous tissue, and platysma in all patients. The skin flap was raised under the parotid fascia to the anterior border of the masseter muscle, and superficial or total parotidectomy was performed in all participating hospitals. In the case with implantation of Megaderm™ (L & C BIO Corp., Seongnam-si, Korea), a 5 cm × 8 cm sheet was used in single-layer grafts or folding grafts according to the surgeon's decision (*Figure 1*). Megaderm™ was trimmed to the proper size and shape based on the size of the depression and inserted between the flap in the parotid bed and the residual parotid tissue. All patients had a Hemo-vac drain inserted during surgery and removed when the amount of drainage was less than 20 cc.

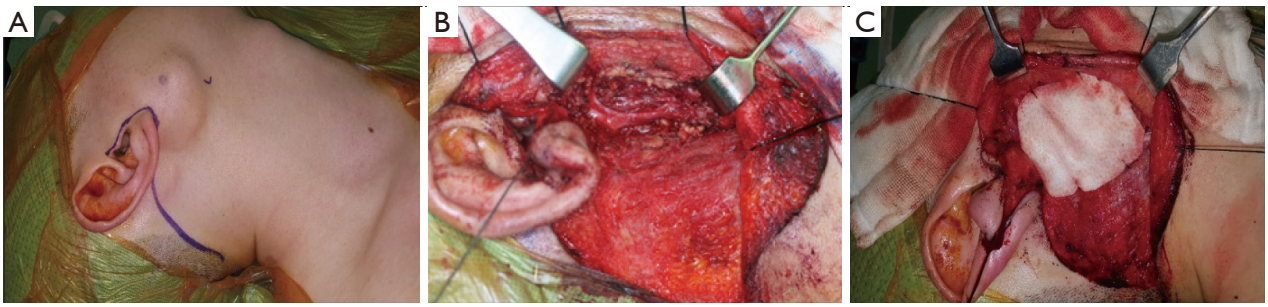

Figure 1 The implantation of ADM (acellular dermal matrix) following total parotidectomy. (A) Preoperative photo shows the modified facelift incision method that was used. (B) Intraoperative view shows the surgical field after total parotidectomy with preservation of the facial nerve. (C) The ADM is designed and inserted between the parotid bed flap and the residual parotid tissue.

Table 1 Clinician evaluation of Frey's syndrome

Variable	Grading [score]
Frey's symptoms	Yes [1]/no [0]
Affected area	0.1–2 cm [1]/2.1–4 cm [2]/>4 cm [3]
Excessive focal sweating	Yes [3]/no [0]
Unpleasant smell	Yes [3]/no [0]
Total score	0–10

Allocation

All of the participants were then allocated into two groups. Half of the enrolled patients underwent parotidectomy with implantation of Megaderm™ (L & C BIO Corp., Seongnam-si, Korea). The other patient group underwent parotidectomy alone without Megaderm™ implantation. The use of Megaderm™ was decided by choice of patients with the recommendation of the surgeon. The surgeon performed the implantation of Megaderm™ only on the agreed patients. The patients purely determined the use of Megaderm™ because of the economic burden of the Megaderm™ and the fact that the external material is inserted into the patient's body.

Outcome measures

Preoperative data including age, gender, body mass index (BMI), underlying disease, allergic history, and pathologic tumor type were collected. Follow-up examinations were carried out at 1 week, and 3, 6, and 12 months postoperatively. The evaluation of acute complications including infection, seroma, hematoma, skin necrosis, and acute parotid area pain was performed 1 week postoperatively. Grading of Frey's syndrome was performed at 3, 6, and 12 months (*Table 1*). The iodine-starch test was performed at each follow-up visit. Objective evaluation of infra-auricular depressed deformities was performed by two independent, blinded physicians using a visual analog scale of contouring deformity based on facial photos taken from the anterior, head-elevating, lateral, and oblique views (1, undetectable deformity; 2, mild deformity; 3, moderate deformity; 4, severe deformity; 5, extremely severe deformity). At 3, 6, and 12 months, each patient also filled in a questionnaire that included a subjective satisfaction score of gross neck appearance (Score 1–5; 5 being the most satisfactory); quality of Frey's syndrome (Scores 1–4: 1, hardly ever; 2, sometimes and tolerable; 3, regular and unpleasant; 4, often and annoying); and acute parotid area pain using a visual analog scale (scores 1–10; 10 being the most severe).

Statistical analysis

An unpaired *t*-test and chi-square test were used for descriptive analysis and Pearson's chi-square test and Fisher's exact test were used for qualitative variables. A P value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software, version 22.0 (IBM Corporation, USA).

Results

Patient characteristics

A total of 134 patients were enrolled, with 25 patients lost to follow-up, 109 patients (58 Megaderm™ group and 51 control group) completing all follow-up examinations. There were 59 males and 50 females with a mean age of 42.5±4.8 years (range, 21 to 67 years). There were no

statistically significant differences in patient characteristics and pathologic distribution of the two groups (*Table 2*).

Acute postoperative complications

Complications were observed in 38/109 (34.8%) patients at 1 week postoperatively. The most common acute complication (20 patients, 18.3%) was seroma (*Table 3*). The rate of seroma complications at postoperative week 1 was significantly higher in the Megaderm™ group compared with the control group. However, there was no significant difference between the groups in the rate of any other complications.

Effect on Infra-auricular depressed deformity

The appearance of the infra-auricular depressed deformity was assessed using a contouring deformity VAS and subjective satisfaction score at 3, 6, and 12 months after parotidectomy. The contouring deformity VAS of the Megaderm™ group compared with the control group was significantly lower at 3, 6, and 12 months. The subjective satisfaction scores of the Megaderm™ group were also significantly higher than in the control group at 3, 6, and 12 months after parotidectomy (*Table 4*).

Effect on Frey's syndrome

According to patients' reported symptoms, 17 (15.5%), 16 (14.6%), and 12 (11%) of the 109 patients experienced Frey's syndrome at 3, 6, and 12 months after parotidectomy, respectively. Significant decreases in the incidence and total clinician calculated Frey's syndrome score at 3, 6, and 12 months after surgery were observed in the Megaderm™ group. However, there was no difference between groups in the patient reported Frey's syndrome quality scores at 3, 6, and 12 months (*Table 5*).

Effect on first bite syndrome

The Megaderm™ group reported significantly lower rates of acute pain during the past 3 months and pain VAS scores compared with those in the control group at 3, 6, and 12 months after parotidectomy (*Table 6*).

Discussion

Parotidectomy is commonly thought to be a burdensome surgery because of potential complications that adversely affect patients' daily life. Common complications associated with parotidectomy are facial nerve injury, facial numbness, asymmetric facial contour, gustatory sweating, and postprandial facial pain (1).

Frey's syndrome and an infra-auricular depressed deformity are two complications that may be prevented by similar methods. Frey's syndrome occurs by the aberrant regeneration of sectioned parasympathetic fibers, which re-grow to the sympathetic nerve fibers that control the subcutaneous sweat glands and vessels. Based on the above pathophysiology, Frey's syndrome is believed to be prevented by blocking aberrant innervations with a barrier between the skin flap and the remnant parotid tissue (6,7). Infra-auricular depressed deformity is almost always observed in total parotidectomy patients due to the loss of profuse parotid tissue. Over the years, various autologous tissue interposition methods have been reported to reduce the incidence of both Frey's syndrome and depressed deformity (6-10). However, autologous tissue interposition has various drawbacks, such as the need for additional donor sites, increased operation time, limited donor sources, and the possibility of postoperative complications and resorption (11).

ADM was first used in full-thickness burns by Livesey *et al.* in 1995 (16). Since then, ADM implantation is gradually replacing autologous tissue interposition owing to the ease of trimming, variability in size and thickness, and avoidance of donor site morbidity in head and neck reconstruction (11,12). However, most studies of ADM in parotidectomy have been retrospective and observational in design. This study is significant as the first multi-center prospective trial to investigate the effect of ADM on chronic complications of parotidectomy.

In this study, the incidence and total Frey's syndrome score following parotidectomy in the Megaderm™ group were significantly lower compared with those in the control group at 3, 6, and 12 months. Also, the objective and subjective evaluation of the facial contour showed a better outcome in the Megaderm™ implantation group compared with those in the control group at 3, 6, and 12 months.

ADM is derived from human cadaveric skin and consists of basement membrane and collagen-based connective tissue without cellular and immunogenic components (17). The main mechanisms of ADM implantation are based on fibroblast infiltration and neo-vascularization. In the application to fill dead space, it induces cellular infiltration by macrophages, finally leading to tissue generation and revascularization within the host (18). ADM has been

Table 2 Patient demographic and clinical characteristics by group

Variables	ADM (n=58)		Control (n=51)		Total (n=109)		P value
	N	%	N	%	N	%	
Sex							
Male	27	46.5	32	62.7	59	54.1	0.066
Female	31	53.4	19	37.2	50	45.8	
Age (years)							
20–29	10	17.2	5	9.8	15	13.7	0.487
30–39	14	24.1	15	29.4	29	26.6	
40–49	12	20.6	13	25.4	25	22.9	
50–59	14	24.1	13	25.4	27	24.7	
60–69	8	13.7	5	9.8	13	11.9	
BMI							
Under weight	1	1.7	0	0	1	0.91	0.287
Normal weight	21	36.2	20	39.2	41	37.6	
Overweight	17	29.3	20	39.2	37	33.9	
Obese	12	20.6	10	19.6	22	20.1	
Extremely obese	7	12	1	1.9	8	7.3	
Smoking							
Yes	13	22.4	16	31.3	29	26.6	0.206
No	45	77.5	35	68.6	80	73.3	
Allergy							
Yes	2	3.40	3	5.8	5	4.58	0.671
No	56	96.7	48	94.1	104	95.4	
Drug hypersensitivity							
Yes	2	3.44	2	3.92	4	3.66	0.308
No	56	96.5	49	96.0	105	96.3	
Operation							
Superficial	58	100	50	98	108	99	0.705
Total	0	0	1	1.96	1	1	
Pathologic diagnosis							
Pleomorphic adenoma	36	62	35	68.6	71	65.1	0.781
Warthin	17	29.3	13	25.4	30	27.5	
Oncocytoma	3	5.17	2	3.92	5	4.58	
Basal cell adenoma	1	1.72	1	1.96	2	1.83	
Miscellaneous	1	1.72	0	0	1	0.91	

ADM, acellular dermal matrix; BMI, body mass index.

Table 3 Surgical complications at 1 week postoperative

Variables	ADM (n=58)		Control (n=51)		Total (n=109)		P value
	N	%	N	%	N	%	
Infection	2	3.44	1	1.96	3	2.75	1.00
Seroma	14	24.1	6	11.7	20	18.34	0.022
Hematoma	5	8.62	4	7.84	9	8.25	0.182
Skin necrosis	0	0	0	0	0	0	
Acute pain	3	5.17	5	9.8	8	7.33	0.28
Allergic reaction	0	0	0	0	0	0	

ADM, acellular dermal matrix.

Table 4 Visual analogue scale for the contouring deformity and subjective satisfaction scores for both patient groups

Contouring deformity	Month 3		Month 6		Month 12	
	ADM	Control	ADM	Control	ADM	Control
1. Undetectable deformity	31	8	25	5	22	4
2. Mild deformity	26	23	32	22	34	23
3. Moderate deformity	4	15	4	16	5	16
4. Severe deformity	0	7	0	10	0	10
5. Extremely severe deformity	0	1	0	1	0	1
SSS	4.26±0.51	3.78±0.97	4.16±0.32	3.63±0.92	3.96±0.54	3.57±0.86
P value (VAS/SSS)	0.001/0.001		0.001/0		0.001/0	

ADM, acellular dermal matrix; VAS, visual analogue scale; SSS, subjective satisfaction score.

Table 5 Patient evaluation of Frey's syndrome in both groups

Variables	Month 3		Month 6		Month 12	
	ADM	Control	ADM	Control	ADM	Control
Patients (%)	3 (5.17)	14 (27.4)	4 (6.89)	12 (23.5)	4 (6.89)	8 (15.6)
Total pain score [0–10]	0.23±1.2	3.48±1.54	0.36±1.31	3.57±1.1	0.28±1.19	3.64±0.85
Frey's quality [1–4]	1.05±0.34	2.13±0.48	1.25±0.24	2.36±0.78	1.32±1.15	1.41±0.78
P value	0.032/0.027/0.095		0.037/0.024/0.315		0.018/0.024/0.287	

ADM, acellular dermal matrix.

Table 6 Evaluation of First bite syndrome pain in parotidectomy patients in both groups

Variables	Month 3		Month 6		Month 12	
	ADM	Control	ADM	Control	ADM	Control
Acute pain in past 3M	1.72±1.17	3.04±2.25	1.48±1.45	4.25±2.73	0.72±1.82	2.85±1.59
Pain VAS	0.90±1.4	2.93±2.0	1.52±1.36	2.571.63	1.02±0.89	1.85±1.38
P value (No./VAS)	0/0.002		0.023/0.01		0.034/0.02	

ADM, acellular dermal matrix; M, month; No., number; VAS, visual analogue scale.

used as an interposition barrier and tissue augmentation substitute in parotidectomy, and the type IV collagen in the dermal matrix serves to block the misconnected in-growth of the nerve fibers (19).

In this study, patients with Megaderm™ implants had less acute pain and a lesser pain VAS score during eating compared with those in the control group at 3, 6, and 12 months. One of the common complications of parotidectomy, First bite syndrome, presents as acute and sharp pain at the first mastication of a meal following parapharyngeal surgery or deep lobe parotid surgery. It is caused by loss of sympathetic innervations to the parotid gland and subsequent cross-stimulation of parasympathetic neurotransmitters released by mastication. There are several treatment options for first bite syndrome, such as medication, tympanic neurectomy, and botulinum toxin type A (BTA) injection. However, efficacy of these therapies has not been fully demonstrated. BTA intra-parotid injection has recently been introduced as the most safe and effective method for the management of first bite syndrome (20). The effectiveness is thought be due to a blockade of the neurotransmitters that induce intense myoepithelial contractions. Similarly, ADM can reduce the intensity and incidence of first bite syndrome by blockage of neurotransmitters.

Our study suggests that Megaderm™ implantation was associated with an increased rate of seroma at 1week postoperatively. The reason for this is uncertain. One hypothesis is that seroma results from a disturbance of saliva reabsorption caused by interactions with Megaderm™ and remnant parotid tissue (17). We suggest that Hemovac use is particularly important to prevent seroma with Megaderm™ implantation.

The primary limitation of this study is the low number of patients with total parotidectomy. Thus, a comparative analysis of superficial and total parotidectomy could not be performed. Moreover, the postoperative follow-up period in this study was 1 year, which may not be adequate to verify the long-term effects of Megaderm™ application and any long-term complications such as resorption and foreign body sensation. Many clinical studies have demonstrated the effectiveness of Megaderm™ for preventing infra-auricular depressed deformities and Frey's syndrome after parotidectomy (11,12). However, this multi-center study is the first to prospectively investigate the usefulness of Megaderm™ in regard to various parotidectomy complications.

Megaderm™ implants are available in various sizes, avoid the problem of donor site morbidity, and lead to fewer complications than parotidectomy without ADM. Megaderm™ implantation in parotidectomy is a safe and effective method for preventing infra-auricular depressed deformity, Frey's syndrome, and first bite syndrome. Megaderm™ implantation may be especially advantageous in complex parotidectomy with significant complications expected.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards of Ajou University, Cheonan Soonchunhyang University, Gangnam Severance Hospital, Inha University, International St. Mary's Hospital, Severance Hospital (No. 4-2014-0848) and informed consent was taken from all individual participants.

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